PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**(CASE NO. MBHB00-203)**

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| **In Re Application of:** | ) | |
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| **Ruderman, et al** | ) | **Examiner: Carolyn Bleck** |
| | ) | |
| **Serial No.: 09,534,946** | ) | |
| | ) | **Group Art Unit: 3626** |
| **Filed: March 24, 2000** | ) | |
| | ) | |
| **Title: CARDIOVASCULAR HEALTHCARE MANAGEMENT SYSTEM AND METHOD** | ) | |

## RULE 132 DECLARATION OF DAVID T. SHEWMAKE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, David T. Shewmake, declare and state as follows:

1. I am an inventor of the above-identified application.

2. I am familiar with analysis of the Berkeley HeartLab data related to LDL IIIa and IIIb and HDL 2b as it relates to subjects with normal LDLC and HDLC and the need for medical treatment.

3. I submitted a Declaration with regard to a related case, Serial No. 10/122,081.

4. The data base relating to LDL subclasses and HDL subclasses is not a publicly available data base. This data base was accumulated at Berkeley HeartLab. At the time the application was filed, there were approximately 954 subjects in the data base. There are now approximately 209,000.

5. I have reviewed U.S. Patent 6,576,471 B2 (Otvos), (Exhibit B). Otvos describes a method for determining 2 subsets of lipid particles by NMR. The method of Otvos described in that patent is not capable of determining in excess of 40% of subjects with normal HDL and LDL levels who are in need of treatment based on subparticle analysis described and claimed in the above-application and which uses a next generation and thus more discriminating technology, "segmented gradient gel electrophoresis". For Berkeley HeartLab there exist two different segmented gel configurations: one for LDL-S3-GGE (3 distinct discontinuous segments) and another for HDL–S10-GGE (10 distinct discontinuous segments). The differentiation of result achieved from the "segmented gradient gel electrophoresis" when compared to the NMR. was described in the presentation entitled **Comparison of Traditional and Alternative Laboratory Methods for the Determination of Lipid Measurements, Lp(a) and LDL Subclass Patterns** as presented at the American Heart Association (AHA) 42nd Annual Conference on Cardiovascular Disease Epidemiology and Prevention, April, 2003 (Exhibit C). The following observations and analyses from this presentation are concluded:

A. NMR technology has never been correlated to the gold standard AnUC (analytical ultracentrifugation) method for describing lipoprotein subclasses. AnUC and the "segmented gradient gel electrophoresis" describe a correlated result for the 7 subclasses of LDL; NMR essentially reports 2 subclasses: Pattern A and Pattern B. Without the 7 subclass discrimination, certain patient samples are misclassified as large LDL molecules "no treatment needed", when in fact they would have been "treatment recommended" i.e., small dense samples if more stringent or "granular" analysis were utilized. This "false negative" treatment conclusion constitutes the essence of the database difference which imposes a significantly varied and more relevant clinical conclusion when using the Berkeley HeartLab database.

B. NMR technology has never been correlated to the gold standard AnUC (analytical ultracentrifugation) method for describing lipoprotein subclasses. AnUC and the "segmented gradient gel electrophoresis" describe a correlated result for the 5 subclassses of HDL; NMR only reports 2 subclasses of HDL: large and small. Within the 5 subclass discrimination, the most significant as an indicator of the status of "reverse cholesterol transport" is HDL 2b. NMR can not accurately discriminate and reproducibly analyze HDL 2b. Without the HDL 2b discrimination, certain patient samples are misclassified as "no treatment needed", when in fact they would have been "treatment recommended" if the more stringent or "granular" analysis of HDL 2b were available and utilized. This "false negative" treatment conclusion constitutes the essence of the database difference with respect to HDL and impaired reverse cholesterol transport. This technology difference imposes a significantly varied and a more relevant clinical conclusion within the Berkeley HeartLab database when compared to NMR.

C. The NMR technology has never been correlated to the gold standard AnUC (analytical ultracentrifugation) method for describing lipoprotein subclasses. AnUC and the "segmented gradient gel electrophoresis" describe a correlated result for the 7 subclassses of LDL; NMR only reports essentially 2 subclasses of LDL: Pattern A or Pattern B. Within the 7 subclass discrimination, the smallest of the subclasses and the most significant as both an indicator of treatment degree of aggressiveness as well as a guide for immediacy of response is LDL IVb. A number of papers and abstracts have been published in the last few years supporting this position. NMR can not accurately discriminate or reproducibly analyze LDL IVb. Without the LDL IVb discrimination, certain patient samples would be either misclassified as "no treatment

needed", instead of "treatment recommended" if the more stringent or "granular" analysis of LDL IVb were available and utilized or would have improper treatment plans resulting in extended treatment, compromised outcomes and/or improper longitudinal clinical data. This "false negative" or degree of aggressiveness treatment conclusion constitutes the essence of the database difference with respect to LDL. This technology difference imposes a significantly varied and a more relevant clinical conclusion within the Berkeley HeartLab database when compared to NMR.

D. In reading through the Otvos patent (Exhibit B) there is no reference to mischaracterizing patients as being healthy compared to NCEP (National Cholesterol Education Program) ATP III guidelines when in fact those patients are in need of treatment. This is the point of our patent application that we discovered with our segmented gradient gel technology and our Berkeley HeartLab database. There does not seem to be a conflict between the Otvos patent and our patent application in terms of mischaracterizing patients as the Otvos patent does not make this comparison to ATP III or address this issue.

E. The Otvos NMR technology described in the 6,576,471 patent is not capable of identifying those patients with normal HDL and LDL who are in need of treatment as described and claimed in this application.

6. That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

March 23, 2005
Date

David T. Shewmake
David T. Shewmake, Ph.D.

## RELATED PROCEEDINGS APPENDIX

None



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